Exhibit A

FISH & RICHARDSON P.C.

225 Franklin Street
Boston, Massachusetts
02110-2804

Telephone
617 542-5070

Facsimile
617 542-8906

Web Site
www.fr.com

Frederick P. Fish
1855-1930

W.K. Richardson
1859-1951

VIA FACSIMILE

March 7, 2005

Examiner Q. Janice Li
U.S. Patent & Trademark Office
Commissioner for Patents
Washington, D.C. 20231

Re: LIVE VACCINES FOR ALLERGY TREATMENT
Appli. No.: 09/778,672
Our Ref.: 12774-002001

AUSTIN
BOSTON
DALLAS
DELAWARE
NEW YORK
SAN DIEGO
SILICON VALLEY
TWIN CITIES
WASHINGTON, DC

Dear Examiner Li:

Thank you for granting a telephone interview, scheduled for 2:30 pm, March 8, 2005 to resolve an issue raised in the final office action and advisory action. As I know you are busy, I will limit the telephone discussion to claim 24. Hopefully, the summary below will facilitate resolving this issue.

Claim 24, rejected for obviousness, is drawn to a method of decreasing the production of IgE in a subject exposed to a dust mite allergen. The method includes orally administering to a subject a non-pathogenic Gram-positive bacterium that contains a nucleotide sequence encoding a dust mite allergen; and expressing the allergen in the bacterium.

You rejected this claim as being obvious over Hsu (which teaches suppressing allergen-specific IgE production in a subject by administering to a subject a recombinant plasmid encoding an allergen) and Janeway (which teaches shifting an antibody response away from an IgE-dominated response towards one dominated by IgG for desensitization) in view of Pouwels and Medaglini (both of which teach using an antigen or allergen expressed by non-pathogenic Gram-positive bacteria for oral immunization). You asserted that it would have been obvious to one skilled person to modify the Hsu's method by replacing the recombinant plasmid with the bacterium taught in Pouwels or Medaglini.

In the response to the final office action, we pointed to a paragraph from Hsu to show that (1) the Hsu's plasmid-based approach relies on the CD8+ T cell-dependent antigen-presenting pathway and suppresses IgE production; and (2) the Pouwels or Medaglini bacterium-based approach relies on the $CD4^+$ T cell-dependent antigen-presenting pathway and supports IgE production. We proceeded to conclude that a skilled person would not use the bacteria taught in Pouwels or Medaglini for suppressing IgE.

You countered that the Hsu paragraph regarding the two pathways is not specific to the above-mentioned two approaches. To elucidate these two pathways, we are attaching three relevant figures from Molecular Biology of the Cell by Bruce Alberts et al., Garland Pub; 4th edition, March 2002 ("Alberts"). (The table appended to this letter shows the features of the two pathways, as well as their implication in IgE regulation as taught in Hsu.)

Figure 24-58 illustrates the antigen-presentation of a foreign protein (e.g., a viral protein) that is generated inside an antigen-presenting cell (APC) of a subject. This "self-made" foreign protein is bound to class I MHC protein and recognized by CD8+ T cells (also see Figure 24-55). Note that Figure 24-58 mirrors the Hsu approach. More specifically, a recombinant plasmid encoding a foreign allergen gene is introduced into an APC. This foreign gene is then transcribed and translated inside the cell, processed through cytoplasm and proreasome, bound to class I MHC protein, and recognized by CD8+ T cells. In contrast, Figure 24-60 represents the Pouwels or Medaglini approach, in which an antigen or allergen is already expressed by bacteria as an extracellular protein to an APC. This extracellular protein is then endocytosed by the cell, processed without going through cytoplasm or proreasome, bound to class II MHC protein, and finally recognized by CD4+ T cells.

In view the above knowledge well known in the art and Hsu's teachings on IgE regulation, a skilled person would recognize that an antigen delivered by the Pouwels or Medaglini bacterium is recognized by CD4+ T cells, which support IgE production. It follows that he or she would not have been motivated to replace the Hsu's recombinant plasmid with the bacteria taught in Pouwels or Medaglini.

Janeway teaches desensitizing by shifting an antibody response away from an IgE-dominated response towards an IgG dominated response. For the same reasons set forth above, a skilled person would have recognized that Janeway's teaching is applicable to the Hsu plasmid-based approach only, but not to the Pouwels or Medaglini bacterium-based approach. In other words, a skilled person would have no reasonable expectation of success to modify Hsu's method in the manner you suggested.

Here, we note that "[t]he test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts." See MPEP 2143.01. Thus, all above-discussed references must be considered. It is improper to consider only Janeway and disregard Hsu or Alberts.

We look forward to discussing with you the above issue at the interview.

Very truly yours,

Jianming Jimmy Hao, Ph.D.
Reg. No. 54,694

Table. Comparison of Two Antigen-presenting Pathways

Figure	Antigen	Cell organelles	Bound to	Recognized by	Examples	IgE
Figure 24-58	A foreign gene is transcribed and translated inside an APC.	Goes through cytoplasm and proteasome	Class I MHC	CD8+ T cells.	Hsu	Suppress IgE production
Figure 24-60	A foreign gene is already expressed as an extracellular protein to an APC.	Does not go through cytoplasm or proteasome	Class II MHC	CD4+ T cells	Pouwels Medaglini	Support IgE production